

Micro-Geographical Heterogeneity in *Schistosoma mansoni* and *S. haematobium* Infection and Morbidity in a Co-Endemic Community in Northern Senegal

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Abstract

Background: *Schistosoma mansoni* and *S. haematobium* are co-endemic in many areas in Africa. Yet, little is known about the micro-geographical distribution of these two infections or associated disease within such foci. Such knowledge could give important insights into the drivers of infection and disease and as such better tailor schistosomiasis control and elimination efforts.

Methodology: In a co-endemic farming community in northern Senegal (346 children (0–19 y) and 253 adults (20–85 y); n = 599 in total), we studied the spatial distribution of *S. mansoni* and *S. haematobium* single and mixed infections (by microscopy), *S. mansoni*-specific hepatic fibrosis, *S. haematobium*-specific urinary tract morbidity (by ultrasound) and water contact behavior (by questionnaire). The Kulldorff's scan statistic was used to detect spatial clusters of infection and morbidity, adjusted for the spatial distribution of gender and age.

Principal Findings: *Schistosoma mansoni* and *S. haematobium* infection densities clustered in different sections of the community ($p = 0.002$ and $p = 0.023$, respectively), possibly related to heterogeneities in the use of different water contact sites. While the distribution of urinary tract morbidity was homogeneous, a strong geospatial cluster was found for severe hepatic fibrosis ($p = 0.001$). Particularly those people living adjacent to the most frequently used water contact site were more at risk for more advanced morbidity (RR = 6.3; $p = 0.043$).

Conclusions/Significance: *Schistosoma* infection and associated disease showed important micro-geographical heterogeneities with divergent patterns for *S. mansoni* and *S. haematobium* in this Senegalese community. Further in depth investigations are needed to confirm and explain our observations. The present study indicates that local geospatial patterns should be taken into account in both research and control of schistosomiasis. The observed extreme focality of schistosomiasis even at community level, suggests that current strategies may not suffice to move from morbidity control to elimination of schistosomiasis, and calls for less uniform measures at a finer scale.

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Introduction

Schistosomiasis is amongst the most common human parasitic diseases with over 230 million people affected worldwide [1]. More than 90% of them live in sub-Saharan Africa [2]. The two major species are *Schistosoma mansoni* and *S. haematobium*, which are co-endemic in many regions [3]. However, little is known about the geographical distribution of both species within such co-endemic regions. Knowledge on micro-geographical variations of single and mixed *Schistosoma* infections and associated disease could provide important insights into the drivers of infection and disease and as such better tailor schistosomiasis control and elimination efforts.

Recent progress in geographic information systems (GIS) has facilitated a better understanding of geospatial dimensions of schistosomiasis on the large scale. On continental and national scales, climatic (e.g. temperature and rainfall) and physical factors (e.g. vegetation, large water bodies, altitude) have been identified as major determinants of the heterogeneous geographical distribution of *Schistosoma* infection (either *S. mansoni* or *S. haematobium*, e.g. [4–13]). On subnational levels, distance to water contact sites, land use and the distribution of infected snails have been reported to contribute to these heterogeneities (e.g. [14–20]).

Few studies have however exploited these techniques to address the geospatial dimensions of schistosomiasis on the micro-scale, i.e.

Author Summary

In the developing world, over 230 million people are infected with parasitic *Schistosoma* worms. *Schistosoma mansoni* and *S. haematobium* are the most abundant species in Africa, affecting the liver and urinary tract, respectively. Both parasites are spread through infested freshwater. Although it is known that the disease occurs focally within countries or regions, little is known on its geographic spread on a smaller scale. Here, we examined 599 people from a community in northern Senegal for *S. mansoni* and *S. haematobium* infections and related abnormalities of the liver and urinary tract. We recorded where they lived and where they had water contact and visualized this information in geographical maps. The study showed that each *Schistosoma* species clustered in a different section of the community, and that liver abnormalities were more severe near the mostly used water contact site. So far, this is the first study to investigate the geographical spread of both species in a single community, and the first to map schistosomal disease on such a small scale. Further studies are needed to confirm and explain these results. They could contribute to a better understanding of schistosomiasis and have important consequences for the control and elimination of this disease.

within communities or among households [21–29]. Most of these considered spatial patterns of only one *Schistosoma* species even though *S. mansoni* and *S. haematobium* often occur together [3]. Moreover, micro-geographical clustering of *Schistosoma* infection has never been studied in relation to *Schistosoma*-specific morbidity.

In the present study, we set out to investigate the spatial patterns of *S. mansoni* and *S. haematobium* infection and morbidity in a co-endemic community on the bank of Lake Guiers in the north of Senegal [30,31]. During the past decades, many communities around Lake Guiers ('Lac de Guiers') in the north of Senegal have become co-endemic for *S. mansoni* and *S. haematobium* [32–35]. *Schistosoma mansoni* was introduced in Richard-Toll in 1988 upon construction of the Diama dam and rapidly spread throughout the region [36,37]. By 1994, virtually the whole Lake Guiers area had become exposed to this species [38]. Today, both *S. mansoni* and *S. haematobium* are wide-spread in the communities around the lake, and the situation is still dynamic.

Methods

Ethics statement

This study was part of a larger investigation on the epidemiology of schistosomiasis and innate immune responses (SCHIS-TOINIR: www.york.ac.uk/res/schistoinir) for which approval was obtained from the review board of the Institute of Tropical Medicine, the ethical committee of the Antwerp University Hospital and 'Le Comité National d'Éthique de la Recherche en Santé' in Dakar. Informed and written consent was obtained from all participants prior to inclusion into the study. For minors, informed and written consent was obtained from the legal guardian.

Participants with severe pathology that needed further treatment were referred to the appropriate health authority. After the study, all community members were offered praziquantel (40 mg/kg) and mebendazole (500 mg) to treat and prevent schistosomiasis and soil-transmitted helminthiasis, respectively [30], according to WHO guidelines [39].

Study area

This cross-sectional study was conducted from July until November 2009 in Diokhor Tack (16°11'24"N 15°52'48"W), the largest community on the Nouk Pomo peninsula in Lake Guiers. Details on the study area have been described elsewhere [30]. In short, it is an isolated, compact and homogeneous Wolof community of Muslim faith with a surface of ~0.25 km². Cultivation is the main means of subsistence and the farmlands that surround the village are irrigated with water from the lake. Although the water from Lake Guiers is piped to the capital city of Dakar, 250 km away [40], the people living nearby do not have access to safe water. Water contact takes place in the lake or in specific sites in canals that are connected to the lake in the west (Figure 1). There were no periodic anthelmintic treatment programs prior to our study and the community does not have a health facility. The nearest 'health post' is ~12 km away. All community members that gave informed consent (or their legal guardians) were included in the study. Participants were registered and recruited from door to door for the parasitological and ultrasound surveys. The community consisted of 71 households, 68 of which participated in this study (Figure 1). This corresponded to a total study population of 599 individuals.

Data collection and definitions

For microscopic diagnosis of *Schistosoma* infection, two feces and two urine samples were collected from each participant on consecutive days. For each feces sample, two Kato-Katz slides of 25 mg fecal material each were prepared, and urine samples were filtered and processed according to standard procedures, as previously described [30,31]. In analogy with earlier micro-geographic studies [21–23], *S. mansoni* and *S. haematobium* infection densities were expressed as the number of eggs detected per gram of feces (epg) or per 10 ml of urine (ep10ml), respectively, including both negative (0 epg or 0 ep10ml) and positive individuals [41]. Single infection was defined as passing eggs of only one species, and mixed infection as passing eggs of both *S. mansoni* and *S. haematobium*, irrespective of the route of egg elimination [30]. *Schistosoma*-specific morbidity was determined by ultrasound, as previously described [31]. Pathologic lesions associated with *S. haematobium* or *S. mansoni* infection were recorded according to the Niamey guidelines [42]. Individuals with signs of hepatic morbidity that were not specific to *S. mansoni* (e.g. hepatitis, cirrhosis or fatty liver) were excluded [42]. To assess the presence or absence of *S. mansoni*-specific hepatic fibrosis, the liver image pattern was determined [42]. Liver image patterns of C ("periportal fibrosis possible") to F ("very advanced periportal fibrosis") were categorized as *S. mansoni*-specific hepatic fibrosis [31]. Individuals with liver image pattern A ("no sign of periportal fibrosis") or B ("incipient periportal fibrosis not excluded") were categorized as controls [42]. To assess the presence or absence of *S. haematobium*-specific urinary tract morbidity, the urinary bladder score was determined [42]. A score of ≥1 was considered as *S. haematobium*-specific bladder morbidity in accordance with previous studies [31,43,44]. The severity of morbidity was represented by the liver image pattern score for *S. mansoni*- and by the upper urinary tract score for *S. haematobium*-specific morbidity [42]. Finally, individual questionnaires were used to explore water contact behavior in a random subsample of people older than 5 years of age.

Mapping and geospatial processing

Water contact sites as well as the center of each household were located using a hand-held differential global positioning system with an accuracy of 3 m (Garmin Etrex H). Household locations

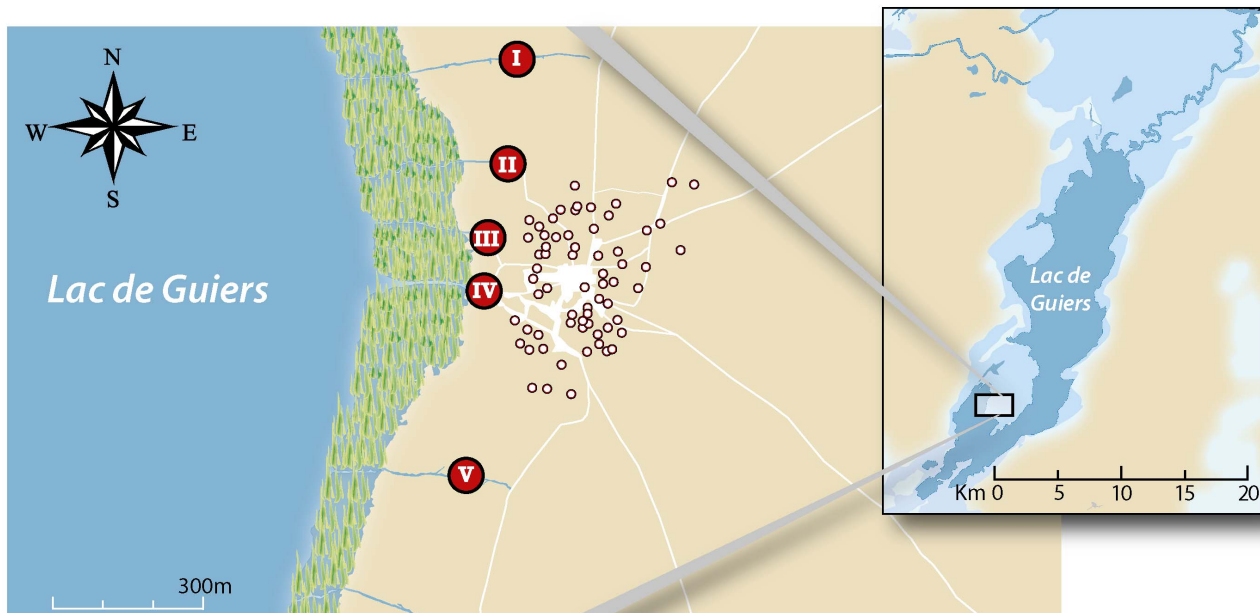


Figure 1. General map of the study village. The inset shows that Diokhor Tack is located in the south-west of the Nouk Pomo peninsula in Lac de Guiers. The main figure indicates the locations of the 68 households that participated in the study (white dots). Red dots with Roman numerals refer to the sites where people come into direct contact with water from the lake. Water contact site III and IV are open spaces enclosed by dense vegetation. Site IV is the largest water contact site. The more remote water contact sites (I, II, and V) are located along irrigation canals in which vegetation was more sparse at the time of study.
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in latitude and longitude were then linked to the collected individual infection, morbidity and questionnaire data (multiple observations per location). These data were imported into SaTScan 9.1.1 (Software for the spatial and space-time scan statistics, developed by M. Kulldorff, Harvard Medical School, Boston and Information Management Services Inc., Silver Spring, Maryland, USA. Available at www.satscan.org) according to the software's user guide [45]. ArcMap 9.3 (ESRI, Redlands, California, USA) was used to project the geographic coordinates and statistically significant clusters (see below) on to the Universal Transverse Mercator zone 28N (1984 datum).

Spatial statistics

The widely used Kulldorff's scan statistic in SaTScan™ tests whether events such as disease cases are distributed randomly in space and, if not, identifies the approximate location of significant geospatial clusters [46]. The test uses a moving circular window that varies up to a predefined size. Each window is a potential cluster. For each window, a likelihood ratio test is applied based on the observed and expected number of cases inside and outside the window to test the null hypothesis of absolute spatial randomness against the alternative hypothesis that there is an elevated risk within the window as compared to outside. The window with the maximum likelihood is the 'most likely cluster'. The p -value of the maximum likelihood ratio test statistic was obtained after 999 Monte Carlo replications. A maximum window size of 50% of the study population was chosen upon sensitivity analysis using maximum sizes from 10 to 50%. Only statistically significant ($p < 0.05$) most likely clusters were reported, and standard settings (i.e. non-overlapping secondary clusters) were used throughout all analyses. In case the most likely (significant) cluster contained only one household, an additional check was performed to increase the robustness of cluster detection. The standard analysis was repeated

while allowing for overlapping secondary clusters (using the "criteria for reporting secondary clusters" option "no restriction = most likely cluster for each grid point" [45]), and the secondary cluster (including the first household) was reported, if it remained significant. Additionally, clusters with $p < 0.06$ were displayed to indicate households that tended to have increased risks.

Infection densities of *S. mansoni* and *S. haematobium* showed skewed distributions, and were therefore normalized by log (base 10)-transformation after adding half of the detection limit to allow for zeros. The detection limit for *S. mansoni* infection was 10 ep_g and that for *S. haematobium* infection 0.5 ep_{10ml}. The spatial distribution of log-transformed infection densities was assessed using normal models [47]. Geometric mean (GM) infection densities in- and outside spatial clusters were computed to quantify significant spatial heterogeneities. Subsequently, Bernoulli models [46] were run to investigate the distribution of single *S. mansoni*, single *S. haematobium* and mixed infections, comparing spatial distributions of people with:

- single *S. mansoni* (1) versus those without single *S. mansoni* infections (0);
- single *S. haematobium* (1) versus those without single *S. haematobium* infections (0);
- mixed (1) versus those without mixed infections (0).

The spatial distribution of the prevalence of hepatic fibrosis and urinary tract morbidity was tested using binary variables in separate Bernoulli models. Ordinal models were used to assess the distribution of the severity of *S. mansoni*- and *S. haematobium*-specific morbidity [48]. Relative risks (RR) comparing people in- and outside clusters, as well as prevalences in- and outside clusters were calculated to quantify significant spatial heterogeneities based on Bernoulli and ordinal models.

Table 1. Characteristics of the 6 datasets used for the gender- and age-adjusted spatial analyses.

Gender	Age (years)	Infection ^a				Morbidity ^a		
		n _{total}	Single <i>S. mansoni</i>	Single <i>S. haematobium</i>	Mixed infections	n _{total}	Hepatic fibrosis	Urinary tract morbidity
Male	0–9	109	15	17	27	49	3	41
Female	0–9	79	9	16	17	28	2	18
Male	10–19	90	21	10	49	49	12	48
Female	10–19	68	11	6	42	34	6	26
Male	≥20	103	39	3	15	49	33	44
Female	≥20	150	44	20	39	82	34	56
Total		599	139	72	189	291	90	233

^aTotal study population in the first columns and numbers of cases in subsequent columns.
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Gender and age are important risk factors for both *Schistosoma* infection [30], and morbidity [31]. To investigate whether these demographic factors 1) caused clustering of infection and morbidity, and/or 2) impacted on the size and exact locations of statistically significant clusters, the abovementioned analyses were adjusted using multiple datasets [49]. Six datasets were prepared, containing either males or females from 0 to 9, 10 to 19, or ≥20 years old (Table 1). SaTScanTM incorporated all datasets into a single log likelihood function. This function is defined as the sum of the individual log likelihoods for those data sets for which the observed case count is more than the expected. Since this adjustment was only possible for the Bernoulli and normal models, separate Bernoulli models were run for the ordinal morbidity model showing significant spatial heterogeneities in the unadjusted analysis.

Finally, Bernoulli models were used to compare the geospatial distribution of people reporting to frequent a particular water contact site *versus* the distribution of people who did not report to frequent that site.

Results

Characteristics of the study population

Complete parasitological data were obtained from a total of 599 individuals from 68 households. The median household size was 8 people (range 1–20). The total study population consisted of 302 males and 297 females with a median age of 15 (range 0–85) years. Ultrasound and questionnaire data were obtained from random subsamples of 291 individuals (64 households), and 277 individuals (63 households), respectively. The prevalence of overall *S. mansoni* infection was 55% (328/599) and that of *S. haematobium* 44% (261/599). Mixed infections were observed in 32% of the population (189/599). The prevalence of *S. mansoni*-specific hepatic fibrosis was 31% (90/291). Most cases had liver image pattern C (71/90), 9/90 had pattern D, while advanced periportal fibrosis was observed in 10/90 cases (nine with liver image pattern E and one with F). The prevalence of *S. haematobium*-specific urinary tract morbidity was 80% (233/291). Positive upper urinary tract scores (range 3–12) were observed in 6% of the study population (18/291). Distributions of single and mixed *Schistosoma* infections, *S. mansoni*-associated hepatic fibrosis and *S. haematobium*-associated bladder morbidity according to gender and age are summarized in Table 1.

Spatial distribution of *Schistosoma* infection

Figure 2A depicts the heterogeneous geospatial distribution of *S. mansoni* and *S. haematobium* infection densities ($p=0.001$ for both

unadjusted analyses). While the size of the *S. haematobium* infection density cluster increased upon correction for the spatial distribution of gender and age, both *S. mansoni* and *S. haematobium* clusters remained statistically significant (Figure 2B; $p=0.002$ and $p=0.023$, respectively).

Participants with mixed and those with single *S. haematobium* infections were randomly distributed ($p=0.16$ and $p=0.080$, respectively), while those with single *S. mansoni* infections tended to cluster geographically (Figure 3A; RR = 1.7; $p=0.053$). Figure 3B indicates that the clustering of single *S. mansoni* was independent of the spatial distribution of gender and age ($p\leq 0.050$), although the cluster size and exact location were slightly altered upon adjustment.

Spatial distribution of *Schistosoma*-specific morbidity

Figure 4A indicates that people with hepatic fibrosis (RR = 1.9; $p=0.054$) and urinary tract morbidity (RR = 1.2; $p=0.053$) tended to cluster in the same area. Adjusted analysis however indicated that these heterogeneous patterns were dependent on the distribution of gender and age ($p=0.087$ for hepatic fibrosis and $p=0.071$ for urinary tract morbidity in the adjusted analysis). In order to assess the distribution of morbidity by severity, ordinal analyses were performed for liver image pattern and upper urinary tract scores. Figure 4B shows that this resulted in one significant cluster ($p=0.001$) in which the RR increased with the severity of hepatic fibrosis: the RR for a healthy liver image pattern A was 0.3, that for B 1.3, for C 1.4, for D 2.7 and for E 4.3. Moreover, the only person with pattern F in the community lived in this cluster. Bernoulli models were used to investigate whether this cluster of severe hepatic fibrosis was independent of the distribution of gender and age. Since more severe hepatic fibrosis was only observed in adults, these analyses were restricted to ≥20-year-olds. Unadjusted Bernoulli models revealed that image patterns D–F (as opposed to A–C) clustered in the households within the hepatic fibrosis cluster that were closest to water contact site IV (RR = 6.3; $p=0.043$; data not shown). The combined distribution of patterns E and F (as opposed to A–D) was homogeneous ($p=0.20$). In the adjusted model, the cluster of pattern D–F remained statistically significant (Figure 4B; $p=0.031$).

The risk of severe urinary tract morbidity was homogeneously distributed ($p=0.38$ in the ordinal analysis).

Water contact behavior

Water contact activities were concentrated at site IV with 62% of the interviewees (172/277) reporting to frequent this site.

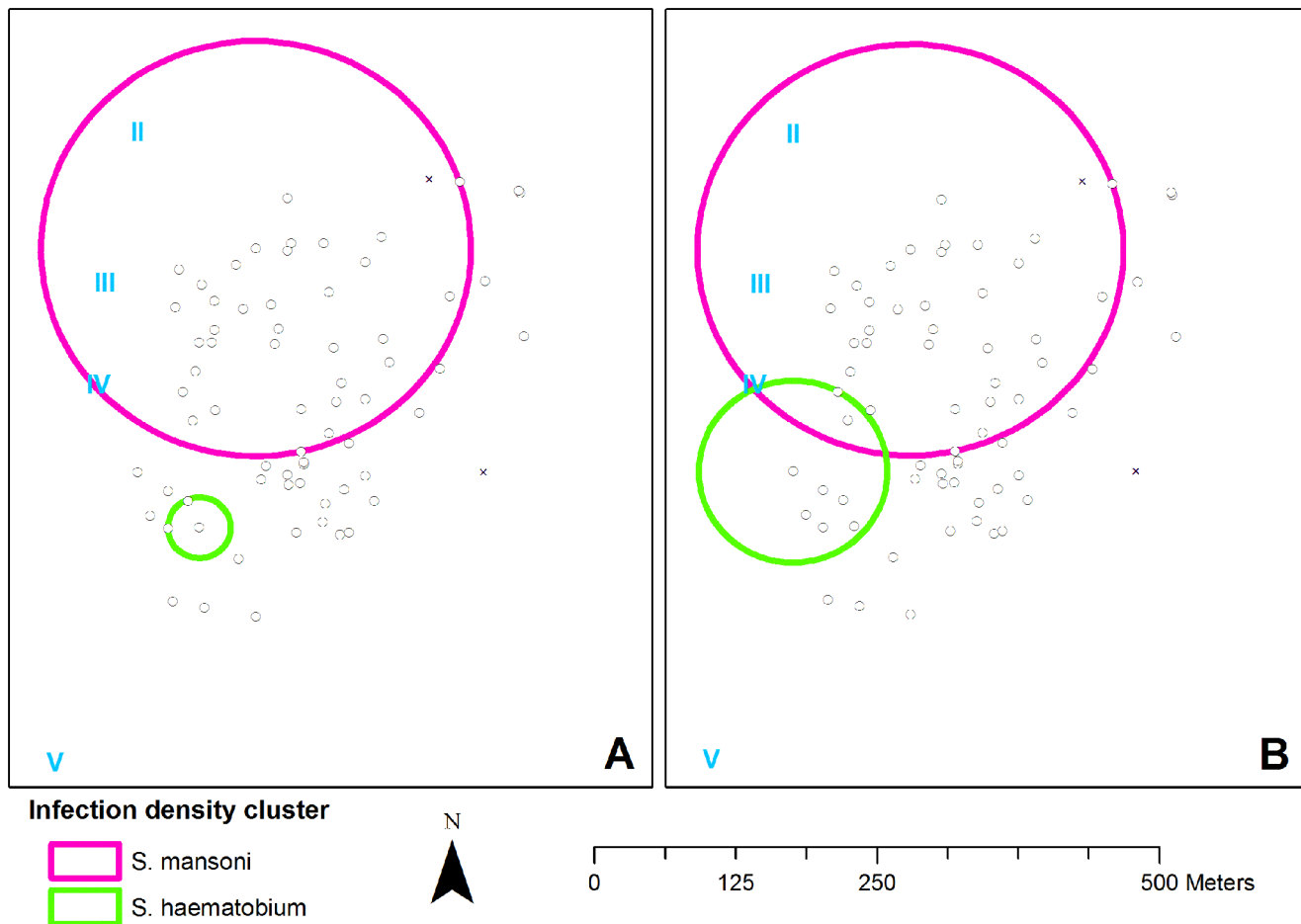


Figure 2. Spatial distribution of *S. mansoni* and *S. haematobium* infection densities. Black circles and crosses indicate households that were included in and excluded from the analysis, respectively. Roman numerals indicate water contact sites. **Panel A** depicts the unadjusted clusters ($p=0.001$ for both *S. mansoni* and *S. haematobium*). The geometric mean (GM) *S. mansoni* infection density was 33 ep_g for those living in inside the northern *S. mansoni* cluster ($n=285$) compared to 12 ep_g in the rest of the community ($n=314$). The GM *S. haematobium* infection density was 4.7 ep_{10ml} inside the southern *S. haematobium* cluster ($n=34$) and 0.7 ep_{10ml} outside ($n=565$). **Panel B** depicts the gender- and age-adjusted clusters ($p=0.002$ for *S. mansoni* (north), and $p=0.023$ for *S. haematobium* (south)). doi:10.1371/journal.pntd.0002608.g002

Numbers of observations in the other sites were limited. Nonetheless, spatial analysis of the questionnaire data revealed significant heterogeneities in the self-reported use of the different water contact sites (Figure 5). People from two adjacent households were more likely to frequent site II than those from the rest of the community (3/4 in- versus 5/273 outside the cluster; $p=0.005$). People living in the center of the community were more likely to frequent site III than others (4/17 versus 2/260; $p=0.022$). Those from the southwest were more likely to frequent site V (8/53 versus 1/224; $p=0.001$). Use of site I and IV did not appear to be linked to a particular group of households ($p=0.31$ and $p=0.16$ respectively).

Discussion

The present micro-geographical study revealed significant clusters of *S. mansoni* and *S. haematobium* infection density in different sections of one community in a co-endemic area, possibly related to heterogeneities in the use of different water contact sites. While the distribution of urinary tract morbidity was homogeneous, a strong geospatial cluster was found for severe hepatic fibrosis. Particularly those people living adjacent to the most

frequently used water contact site were more at risk for advanced morbidity than those living farther away.

These findings confirm the well-known focality of schistosomiasis [50]. Even within one community, one cannot assume the risk of schistosomiasis to be homogenous. More remarkably even, the two *Schistosoma* species clustered in different sections of the community; *Schistosoma mansoni* infections clustered in the north while *S. haematobium* clustered in the south. A series of recent GIS studies showed significant micro-geographical heterogeneities in *S. haematobium* infection within a mono-endemic Kenyan community [21,22]. Those in *S. mansoni* mono-endemic communities showed conflicting results with heterogeneous spatial patterns in some studies and homogeneous patterns in others [24–29]. To our knowledge, only Farooq *et al* have so far investigated the spatial distribution of both infections in a co-endemic community in Egypt in the 1960s. They reported higher infection levels of *S. mansoni* in small children in one section of the community and higher levels of *S. haematobium* in another section [51]. This is in agreement with the divergent distributions of *S. mansoni* and *S. haematobium* infection densities observed in the present study. Several interrelated factors may underlie these observations, and are discussed below.

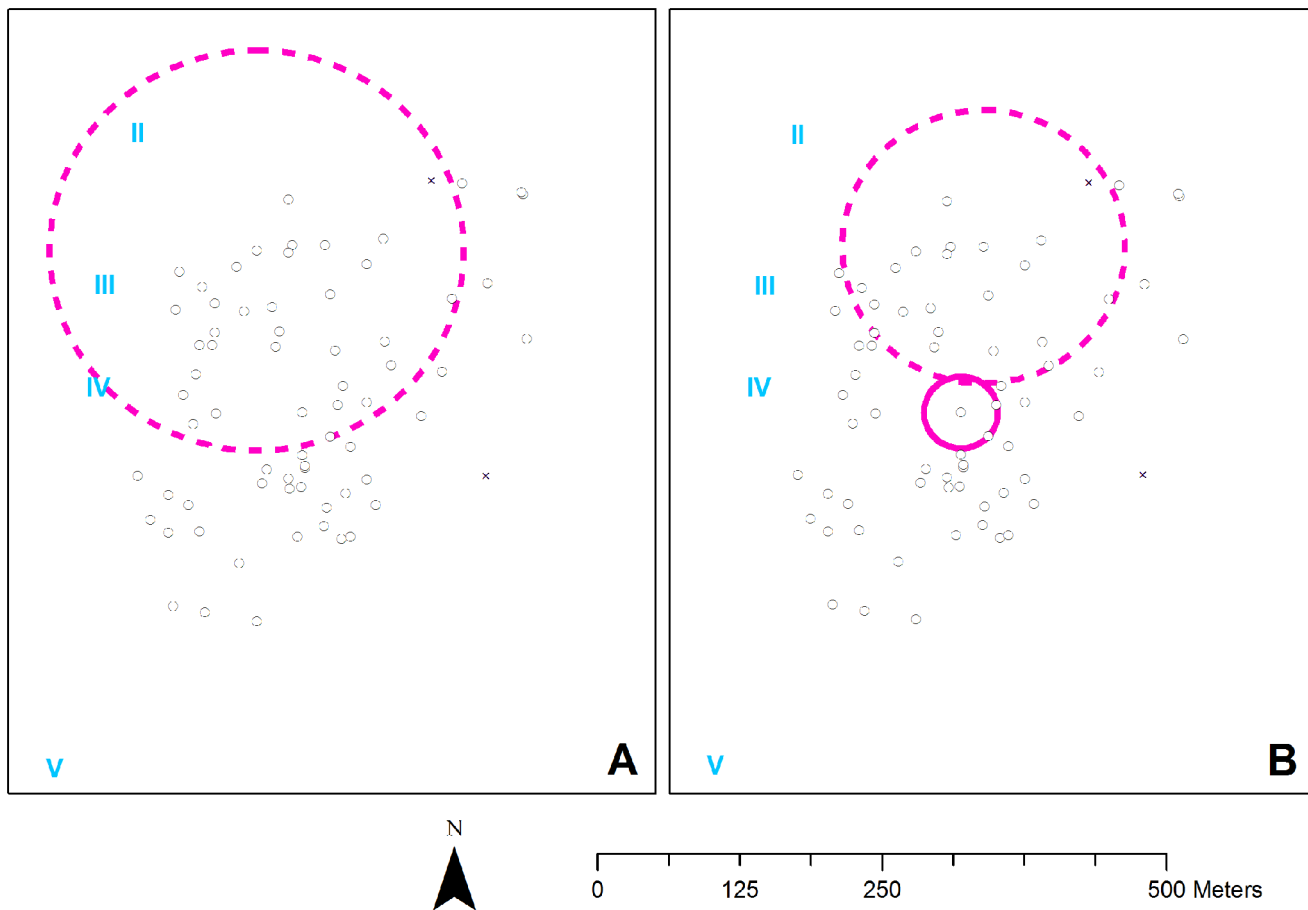


Figure 3. Spatial distribution of single *S. mansoni* infections. Black circles and crosses indicate households that were included in and excluded from the analysis, respectively. Blue Roman numerals indicate water contact sites. Continuous pink circles are statistically significant clusters ($p < 0.05$) and dotted circles are borderline significant ($p < 0.06$). **Panel A** depicts the unadjusted cluster ($RR = 1.7$; $p = 0.053$). The prevalence of single *S. mansoni* infection was 30% (83/278) inside and 17% (56/321) outside the cluster. **Panel B** shows the gender- and age-adjusted clusters ($p = 0.045$ for the most likely cluster (center) and $p = 0.050$ for the secondary cluster (north)). doi:10.1371/journal.pntd.0002608.g003

First of all, the micro-geographic distributions of the intermediate snail host of *S. mansoni* and *S. haematobium*, which belong to the genus *Biomphalaria* and *Bulinus*, respectively, may be divergent as well. Unfortunately, it was logistically impossible to collect snails in the present study. Yet, it is known that these snail species prefer different niches and that their distribution is influenced by chemical, physical, and biological factors [52–57]. Indeed, Woolhouse and Chandiwna demonstrated that the snail hosts of *S. mansoni* and *S. haematobium* occupy different locations in one single habitat in a co-endemic focus [53]. Ecological factors may thus have favored *S. mansoni* transmission in the north and *S. haematobium* transmission in the south.

At the human host level, behavioral factors may have played a role in the observed spatial pattern of infection. Although based on a small number of observations, our questionnaire data indeed indicated that people from the north and center were more likely to frequent the northern sites than other community members, whereas those from the southwest were more likely to use the southernmost site. It thus seems that the first group maintained *S. mansoni* transmission in the north and the second *S. haematobium* transmission in the south. This corresponds to the study of Woolhouse and Chandiwna reporting 1) a similar geospatial segregation of *S. mansoni* and *S. haematobium* infection in the snail host population between transmission sites, and 2) a very focal

man-to-snail transmission, within a distance of 40 m. Interestingly, they proposed that these divergent patterns most likely reflected differences in the distribution of defecation from that of urination, favoring *S. mansoni* and *S. haematobium* transmission, respectively [53]. In contrast to water contact behavior, age and gender of the human host were shown to have a negligible impact on the divergent pattern of *S. mansoni* and *S. haematobium* infection. Spatial clustering in the different sections of the community remained significant upon correction for age and gender. Other factors that may have contributed to the spatial pattern include genetic differences in susceptibility to infection [58–60]. Indeed, extended families tended to live together in this community (L. Meurs, personal observation). Also, people from the same section/extended family are more likely to have similar behavioral patterns [51,61–63].

In contrast to the spatial distribution of *S. haematobium* infection, the distribution of *S. haematobium*-associated urinary tract morbidity was homogeneous. This was unexpected as *S. haematobium* infection has consistently been reported as an independent risk factor for urinary tract morbidity [43,44,64–71]. The fact that *S. haematobium* was only introduced in this region approximately 6 years prior to this study [72], may explain the relatively low severity of urinary tract morbidity in this community and the consequent absence of a spatial pattern. The severity of urinary tract morbidity is expected

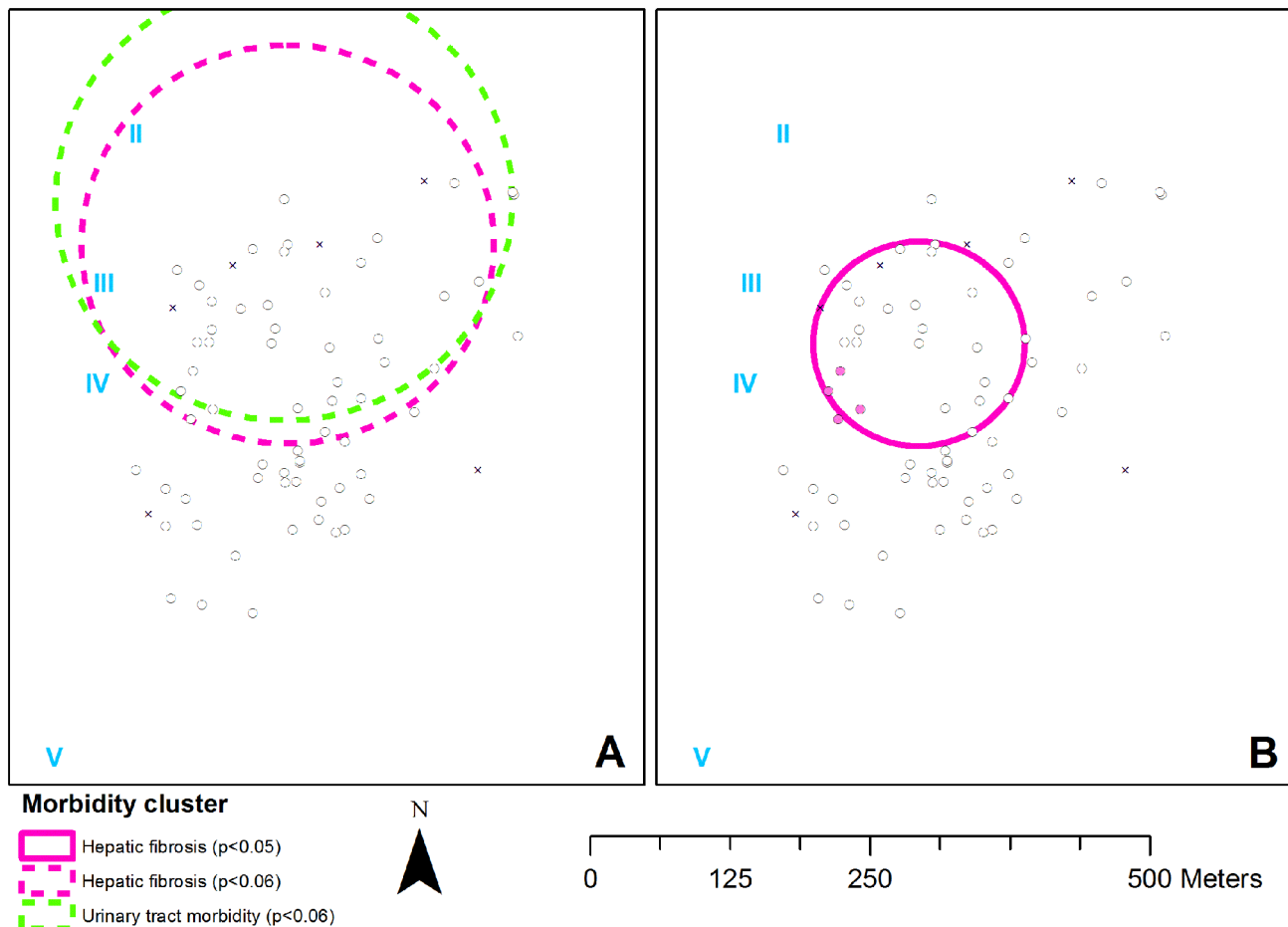


Figure 4. Spatial distribution of *S. mansoni*- and *S. haematobium*-specific morbidity. Black circles and crosses indicate households that were included and excluded from the analysis, respectively. Continuous colored circles are statistically significant clusters ($p < 0.05$) and dotted circles are borderline significant ($p < 0.06$). Roman numerals indicate water contact sites. **Panel A** depicts the unadjusted clusters for the prevalence of morbidity. Both *S. mansoni*-specific hepatic fibrosis (pink dotted circle; $RR = 1.9$) and *S. haematobium*-specific urinary tract morbidity clusters (green dotted circle; $RR = 1.2$) were borderline significant ($p = 0.054$ and $p = 0.053$, respectively). The prevalence of hepatic fibrosis was 41% (59/145) in- and 21% (31/146) outside, and that of urinary tract morbidity was 89% (117/131) in- and 73% (116/160) outside the cluster. Gender- and age-adjusted analysis revealed no (borderline) significant clusters for the prevalence of morbidity. **Panel B** depicts the clusters of morbidity by severity. The risk of severe hepatic fibrosis was elevated in the circle with a RR of 0.3 for liver image pattern A, 1.3 for B, 1.4 for C, 2.7 for D and 4.3 for E, and the only person with pattern F lived here ($p = 0.001$; unadjusted ordinal model). The gender- and age-adjusted cluster for patterns D–F (as opposed to A–C) in adults constituted of the households indicated in pink ($p = 0.031$; Bernoulli model). doi:10.1371/journal.pntd.0002608.g004

to progress over time with cumulative exposure to *S. haematobium* eggs [73].

On the other hand, a strong geospatial cluster was found for severe *S. mansoni*-specific hepatic fibrosis which overlapped with that of *S. mansoni* infection density. At first sight, this seems to be in contrast with previous studies by this group showing that current *S. mansoni* infection is not associated with hepatic fibrosis [31], which usually develops after 5–15 years of exposure [3]. However, a closer look at the overlapping clusters showed that teenagers had the highest infection densities and contributed most to the *S. mansoni* infection density cluster (data not shown). Adults on the other hand had more advanced morbidity, and contributed most to the severe hepatic fibrosis cluster. This suggests that these adults were in fact the teenagers with the highest *S. mansoni* infection densities earlier in life.

Moreover, the clustering of severe hepatic fibrosis in adults seemed to be associated with the distance to the water. Those living within ~100 m of the major water contact site (Figure 4B) were at least six times more likely to develop advanced hepatic

fibrosis (liver image pattern D–F) than those living further away. However, other factors cannot be excluded such as genetic predisposition [74], diet or nutritional status [75], or co-infections, which may have put those living in close vicinity of the water at a higher risk of developing hepatic morbidity than the rest of the community.

To our knowledge, only Booth *et al* have so far investigated micro-geographical variations in *Schistosoma*-associated morbidity. They found an association between splenomegaly and the combined exposure to *S. mansoni* and *Plasmodium falciparum* but did not explicitly investigate spatial clustering [76].

To our knowledge this is the first study to quantify micro-geographical infection patterns of *S. mansoni* and *S. haematobium* in a co-endemic community, and the first to relate these to patterns of *Schistosoma*-specific morbidity. Apart from the strengths, it is also important to address some limitations of our study. First, the study was cross-sectional and the results were merely descriptive in nature. The present study was a first attempt to describe patterns of schistosome infection and morbidity on a micro-scale, and it was

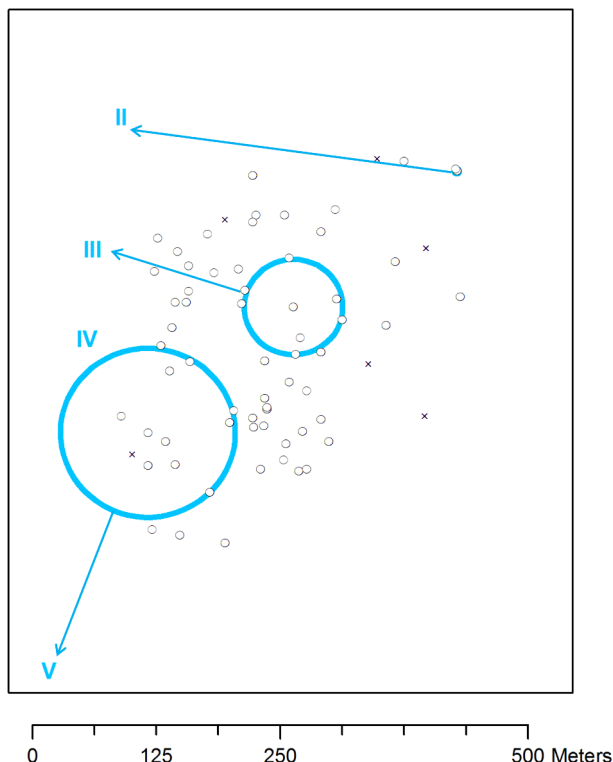


Figure 5. Spatial distribution of self-reported use of the different water contact sites. Black circles and crosses indicate households that were included and excluded from the analysis, respectively. Roman numerals indicate water contact sites. Blue circles indicate clusters of people that reported to frequent a given water contact site indicated by an arrow. Participants in the northeastern cluster were more likely to frequent site II (3/4 versus 5/273; $p=0.005$), participants in the middle cluster to frequent site III (4/17 versus 2/260; $p=0.022$), and those from the southwestern cluster to frequent site V (8/53 versus 1/224; $p=0.001$) than those living outside the respective clusters.

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not designed to explain the underlying mechanisms of potential micro-geographical clustering. Based on the limited data that were available, we generated a number of hypotheses, but other risk factors, including environmental, malacological, genetic, immunological and socio-economic factors, should be included in future studies. In addition, more spatial as well as spatio-temporal studies [21–23] are necessary to confirm our observations in other geographical areas and to explain them. Another limitation was

that there is as yet no standard technique available to investigate spatial patterns. The emergence of various statistical methods has greatly boosted geospatial studies on schistosomiasis and increased our understanding of this disease. On the other hand, the large variety of methods has also hampered the comparison between the different micro-geographical studies that have been conducted so far and standardization is recommended.

Current WHO schistosomiasis control strategies aim to prevent morbidity in later life through regular mass drug administration (MDA) to at risk populations in so-called homogeneous ecological zones [77,78]. However, the strong micro-geographical clustering of infection and morbidity observed in the present study suggests that less uniform strategies should be developed to better tailor control efforts at the local level. A more targeted approach will be even more relevant in view of resolution WHA65.21 on the elimination of schistosomiasis, recently adopted by the WHO [77]. It is expected that MDA alone cannot break the *Schistosoma* life cycle and that complementary interventions will have to be put in place [79]. Micro-geographical studies will help to get much needed insights into local transmission dynamics of *S. mansoni* and *S. haematobium* and hence to develop sustainable control and elimination strategies [80].

Supporting Information

Checklist S1 STROBE Checklist.
(DOC)

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Author Contributions

Conceived and designed the experiments: KP SM TH LM. Performed the experiments: LM MM KV NB FvdB. Analyzed the data: LM KP EA. Contributed reagents/materials/analysis tools: KP TND SM. Wrote the paper: LM KP.

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